

Electrocardiograms of Nine Species of Nonhuman Primates Sedated with Ketamine

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SUMMARY

Electrocardiograms were studied in nine species of nonhuman primates sedated with ketamine hydrochloride. Electrocardiographic values were similar in all species although heart rate and other rate-related values (QT and PR intervals) were species-dependent. Arrhythmias were infrequent. Ketamine hydrochloride did not appear to induce marked alterations in the ECG of primates.

Information is available on the normal ECG of several species of subhuman primates,¹⁻¹² but is scanty¹³⁻¹⁶ or lacking for other species. Normal ECG for nonanesthetized primates^{1,3,7,9-11} and those anesthetized with ether,¹³ phencyclidine hydrochloride,^{6,15} thiopentone sodium,^{5,12} and sodium pentobarbital^{12,18} have been reported. Little data are available on the ECG of primates sedated with the commonly used drug, ketamine hydrochloride.¹⁷ Ketamine has been studied at different dosage levels and routes of administration with only minimal cardiovascular effects.¹⁸⁻²¹

The purpose of the present report was to study ECG values of nine species of subhuman primates sedated with ketamine. Data are compared with findings in those species previously reported.

Materials and Methods

One hundred cynomolgus macaques (*Macaca fascicularis*), 100 squirrel monkeys (*Saimiri sciureus*), 100 African green monkeys (*Cercopithecus aethiops*), 70 stump-tail macaques (*Macaca arctoides*), 50 patas monkeys (*Erythrocebus patas*), 25 rhesus macaques (*Macaca mulatta*), 13 capuchin monkeys (*Cebus apella*), 9 bonnet macaques (*Macaca radiata*), and 8 pigtail macaques (*Macaca nemistrina*) of both sexes were used in this study.

The patas, stump-tail, African green, and squirrel monkeys were maintained in the primate colony at Litton Bionetics, Kensington, Md. The other species were maintained at the US Army Medical Research Institute of Infectious Diseases, Frederick, Md. The animals were fed a commercial diet^a and water ad libitum and were considered to be healthy at the time of study.

The animals were sedated with 10 mg of ketamine hydrochloride^b/kg of body weight IM and a six-lead ECG (leads I, II, III, aVR, aVL, and aVF) was recorded.^c Tracings were standardized at 1 cm = 1 mV, and the paper speed was set at 50 mm/s. Tracings were analyzed for heart rate (HR), mean electrical axis (MEA), P-wave amplitude and duration, PR interval, R-wave amplitude, QRS duration, and QT interval. Lead II tracings were used for wave voltage measurements.

Mean ECG values for each species were compared with all other species, using the least significant difference procedure; the level of significance set at $P = 0.01$. The slope of HR vs QT interval and the confidence interval were computed for each species. Those species with similar slopes ($P = 0.001$) were combined.

Results

General—Significant sex or weight differences were not seen in ECG patterns within the species studied.

Normal sinus rhythm was usually

seen, with occasional sinus arrhythmia noticed only in rhesus macaques (3 of 25). The arrhythmia was seen at slower HR of 126 to 156 beats/minute. Results are summarized (Table 1). The ECG of a normal African green monkey is shown (Fig 1).

Heart Rate—The mean HR of the rhesus, bonnet, cynomolgus, and pig-tail macaques were similar, being 178 ± 29 , 193 ± 26 , 203 ± 29 , 209 ± 30 beats/minute, respectively. The mean HR of the stump-tail macaques (156 ± 19) was significantly lower ($P < 0.01$) than was that of the other *Macaca* spp studied. The HR of African green, capuchin, and squirrel monkeys were 181 ± 41 , 230 ± 27 and 250 ± 44 , respectively. The patas monkeys had a much lower HR of 152 ± 24 .

Mean Electrical Axis—The MEA of all the species studied were not significantly different ($P > 0.01$). The mean MEA for the five *Macaca* spp ranged from 54 to 69 degrees. Of the cynomolgus monkeys, 84% had a MEA between + 40 and + 90 degrees; 70% between + 60 and + 90 degrees. The range was + 150 to - 60 degrees. A tendency toward left axis deviation was seen in this species because 11% of the cynomolgus macaques had a MEA of + 30 degrees or less.

The MEA for the African green monkeys was directed more to the left than were the MEA for the other species studied (mean, 47 ± 27 degrees), with 29% being + 30 degrees or less. In this species, only 52% had MEA between + 60 and + 90 degrees. The range was + 90 to - 67 degrees.

The mean MEA of the patas monkeys was directed more to the right than were the MEA for the other species (75 ± 15 degrees). The range was + 15 to + 90 degrees, 96% being between + 60 and + 90 degrees.

Right axis deviation (MEA > 90 degrees) was seldom seen. Four cy-

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^a Ralston Purina Co, St Louis, Mo.

^b Ketalar, Parke, Davis & Co, Detroit, Mich.

^c Model 5, Burdick Corp, Milton, Wis.

TABLE 1—Electrocardiography of Nine Species of Nonhuman Primates

Species (n)	HR (beats/min)	MEA (degrees)	P-Wave		PR interval (s)	R-Wave amplitude (mV)	QRS duration (s)	QT interval (s)
			Amplitude (mV)	Duration (s)				
<i>Macaca fascicularis</i> (100)	203 ± 29	85 ± 22	0.16 ± 0.05	0.03 ± 0.01	0.08 ± 0.01	0.7 ± 0.3	0.03 ± 0.01	0.19 ± 0.02
<i>M. arctoides</i> (70)	156 ± 19	54 ± 25	0.08 ± 0.03	0.02 ± 0.01	0.09 ± 0.01	0.3 ± 0.2	0.03 ± 0.01	0.22 ± 0.02
<i>M. mulatta</i> (25)	178 ± 29	69 ± 16	0.20 ± 0.05	0.04 ± 0.01	0.09 ± 0.01	0.8 ± 0.3	0.03 ± 0.01	0.20 ± 0.02
<i>M. radiata</i> (9)	193 ± 26	58 ± 23	0.18 ± 0.07	0.03 ± 0.01	0.08 ± 0.01	0.6 ± 0.2	0.03 ± 0.01	0.18 ± 0.02
<i>M. nemestrina</i> (8)	209 ± 30	60 ± 32	0.17 ± 0.05	0.03 ± 0.01	0.07 ± 0.01	0.5 ± 0.2	0.02 ± 0.01	0.16 ± 0.02
<i>Saimiri sciureus</i> (100)	250 ± 44	56 ± 22	0.17 ± 0.05	0.03 ± 0.01	0.06 ± 0.01	0.9 ± 0.4	0.02 ± 0.01	0.15 ± 0.01
<i>Cercopithecus aethiops</i> (100)	181 ± 41	47 ± 27	0.19 ± 0.09	0.03 ± 0.01	0.09 ± 0.01	1.2 ± 0.6	0.03 ± 0.01	0.19 ± 0.03
<i>Erythrocebus patas</i> (50)	152 ± 24	75 ± 15	0.21 ± 0.10	0.04 ± 0.01	0.11 ± 0.01	1.4 ± 0.3	0.03 ± 0.01	0.21 ± 0.02
<i>Cebus apella</i> (13)	230 ± 27	58 ± 31	0.35 ± 0.12	0.03 ± 0.01	0.08 ± 0.01	0.9 ± 0.3	0.02 ± 0.01	0.15 ± 0.01

Data are expressed as mean ± SD. HR = heart rate; MEA = mean electrical axis; n = no. of animals.

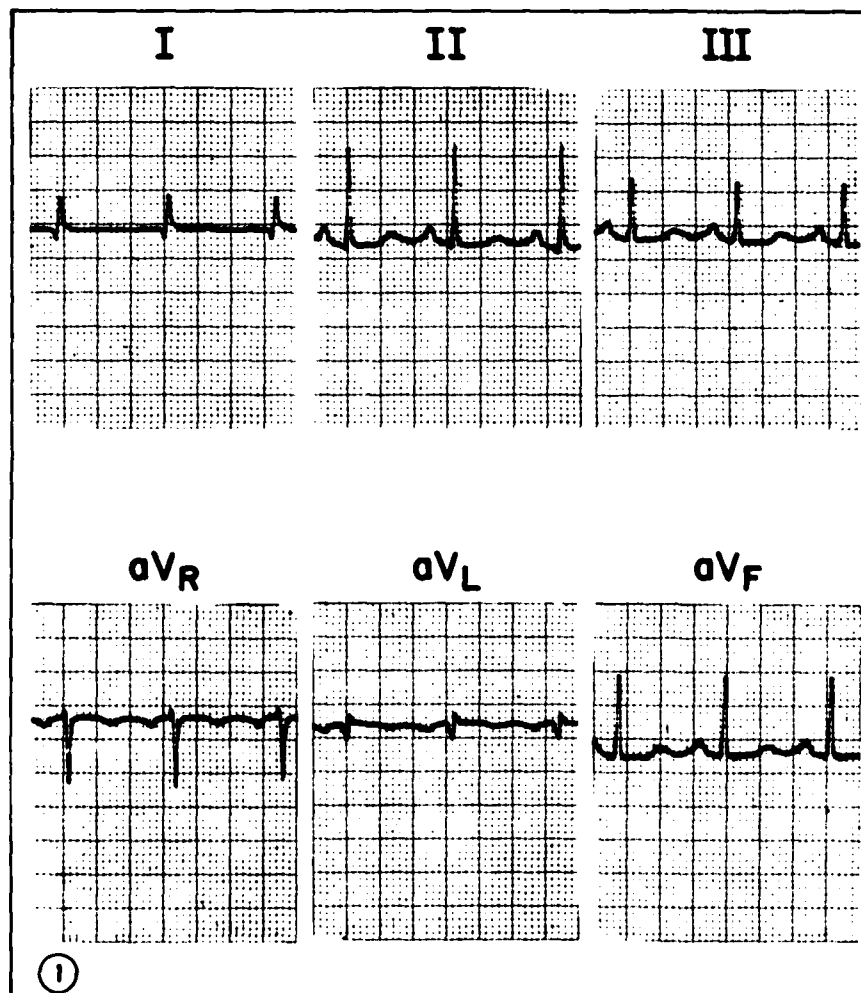


Fig 1—An ECG of a clinically normal African green monkey. Paper speed = 50 mm/s, 1 cm = 1 mV.

nomolgus macaques had MEA greater than + 90 degrees, three with + 120 degrees, and one with + 150 degrees.

P-Wave—The P-wave amplitude in the nine species studied ranged from 0.08 mV in the stumptail macaques to 0.35 mV in the capuchin monkey, which was significantly higher than it was in the other species.

Low voltage tracings were characteristic of all stumptail macaques. The range of the P-wave amplitude was 0.05 to 0.15 mV. P pulmonale (> 0.4 mV) was noticed in 46% of the capuchin monkeys and in one cynomolgus macaque. P-wave duration was longest in the rhesus and patas species (0.04 ± 0.01 s) and shortest in the stumptail macaques (0.02 ± 0.01 s).

Both were significantly different from durations in other species which had mean P-wave durations of 0.03 ± 0.01 s.

PR Interval—The AV conduction time was shortest in squirrel monkeys (0.06 ± 0.01 s) and longest in patas monkeys (0.11 ± 0.01 s). The PR interval tended to increase with decreased heart rate.

R-Wave—The average R-wave amplitude varied considerably with the species studied. The stumptail macaques had low voltage tracings (0.3 ± 0.2 mV), but these values were not significantly different from the values in other species. The maximum R-wave amplitude in this species was 0.7 mV; 64% were less than 0.4 mV. The other macaques had R-wave amplitudes ranging from 0.5 to 0.8 mV. The squirrel and capuchin monkeys had R-wave amplitudes of 0.9 mV. The African green and patas monkeys had the highest average R-wave amplitude of 1.2 ± 0.6 and 1.4 ± 0.3 mV, respectively.

QRS Duration—The duration of the QRS complexes varied little in the different species. The pigtail, capuchin, and squirrel monkeys had QRS durations of 0.02 ± 0.01 s. The other species had QRS durations of 0.03 ± 0.01 s. The range of the means of all species was from 0.01 to 0.04 s. One cynomolgus macaque had a QRS duration of 0.06 s. Several monkeys with longer QRS complexes (0.04 to 0.06 s) had complexes characterized by wide, slurred S waves in leads II, III, and aVF. In these monkeys, the MEA was directed to the left (0 to - 60 degrees).

QT Interval—The mean duration of electrical systole increased as the heart rate decreased. The squirrel and capuchin monkeys, HR = 250 and 230, respectively, had the shortest QT interval (0.15 ± 0.01 s). The longest

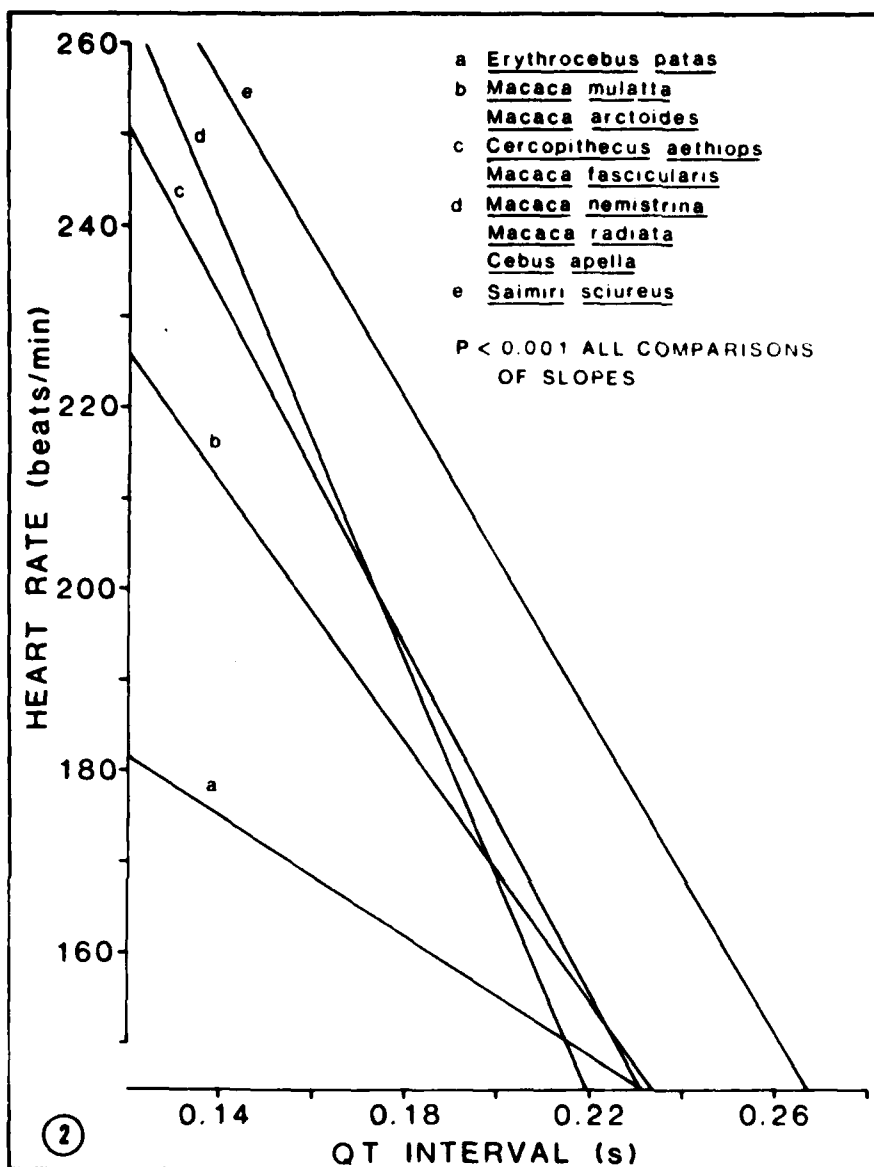


Fig 2—Relationship of QT interval and HR in nine species of monkeys. Species with similar slopes ($P > 0.001$) were grouped together.

mean QT interval (0.22 ± 0.02 s) was in the stump-tail macaque (HR = 156). The relationship of the QT interval to the HR is shown (Fig 2). There were significant ($P < 0.001$) species differences in the slopes derived from the data. Rhesus and stump-tail macaques did not differ significantly ($P = 0.001$), nor did the cynomolgus and African green monkeys. The bonnet, pigtail, and capuchin monkeys were not significantly different from each other.

T-Wave—The T-wave of the monkeys studied was usually positive in leads I, II, III, and aVF. The T-wave was frequently isoelectric in leads I and III, but was seldom so in II and

aVF. It was usually inverted in aVR and frequently inverted in aVL. Inverted T-waves in lead II were noticed infrequently.

Abnormal Tracings—The frequency of abnormal ECG in the species studied was low. Low voltage recordings (R-wave < 0.4 mV in lead II) were noticed in 64% of the stump-tail monkeys, 44% of the bonnet macaques, 38% of the pigtail macaques, 12% of the rhesus macaques, and 13% of the squirrel monkeys.

Premature ventricular contractions were seen occasionally in rhesus macaques and squirrel monkeys. Premature beats occurred singly and ap-

peared to be from one ectopic focus. Incomplete left bundle branch block was noticed in one cynomolgus macaque and in one African green monkey. Right bundle branch block was seen in one capuchin monkey and in one squirrel monkey.

Discussion

General—Significant ($P = 0.01$) sex or weight differences in ECG patterns were not seen. This agrees with data reported for the bonnet macaque,¹¹ the squirrel monkey,¹² the Japanese macaques,^{7,8} the Celebes ape,⁹ and the rhesus macaque.¹³ Sinus arrhythmia was noticed in three of 25 rhesus macaques. This arrhythmia is generally uncommon in monkeys, but has been reported in rhesus macaques with slower heart rates (less than 150/minute).^{14,15,21}

Heart Rate—The HR of the cynomolgus monkey (203 beats/minute) was somewhat higher than that reported by Toback et al.¹¹ (179 beats/minute) and was lower than that reported by DeWaaert and Storm¹⁶ (225 beats/minute). This may be a reflection on the greater number of monkeys used in this study. The mean HR of rhesus macaques in this study (178 beats/minute) was similar to anesthetized monkeys, as reported by others.^{6,22}

The HR of the squirrel monkey (250 beats/minute) was higher than the HR in other species studied, but corresponds to that reported by Wolf et al.¹² (248 beats/minute) in sodium thiopental anesthetized squirrel monkeys.

Previous data on the pigtail macaque were not available, but the HR noticed in the present study was similar to that reported for the Japanese macaque, *M. fuscata*.⁷ The mean HR of the stump-tail macaque (156 beats/minute) was within the range reported by Malhotra et al.²³ The mean HR of the capuchin monkey has been reported to be 220 beats/minute.¹¹ Monkeys in the present study had a mean HR of 230 ± 27 . The mean HR of the bonnet macaques in this study (193 beats/minute) was within the range reported by Rahaman et al.¹¹ The mean HR of the African green and patas monkeys was 181 and 152 beats/minute, respectively. Other data are not available on these species. The normal resting HR of caged monkeys is probably considerably lower than

values reported in the present study. Malinow et al²¹ reported HR as low as 86 beats/minute in rhesus macaques, recorded by an ECG transmitter, but noticed extremely high HR (257 beats/minute) in restrained, nonanesthetized rhesus macaques.³ Because of the increase in HR due to handling before induction, a relative decrease in HR was noticed during ketamine anesthesia, as has been observed in man similarly anesthetized.

P-Wave—The P-wave duration of the nine species studied ranged from 0.02 to 0.04 s, and corresponds with previous reports.^{3,12,15} P-pulmonale was noticed in several monkeys, as has been previously reported,^{1,3,7,12} and is probably a normal variant. It was most often seen in the capuchin monkeys in this study.

Mean Electrical Axis—The MEA of the cynomolgus monkeys was similar to that seen before.^{15,16} As in previous studies, a tendency toward left axis deviation was noticed in the cynomolgus macaque. Frequent left axis deviation also has been reported in the Celebes ape,⁹ in which 37% of the apes studied had a MEA less than 0 degrees.

The MEA of rhesus monkeys was directed slightly more to the right than it was in the other species, as has been previously reported.³ This was also noticed in the patas monkeys although severe right axis deviation did not occur. The MEA of the bonnet and pigtail macaques was similar to the MEA in cynomolgus macaques, but left axis deviation was uncommon.

PR and QT Intervals—Wandering pacemakers were not noticed as had been reported.¹⁴ As seen in Japanese,⁷ cynomolgus,¹⁵ and rhesus macaques,³ baboons,¹⁰ and squirrel monkeys,¹² the PR and QT intervals decreased with an increase in HR in all the species studied, although definite species differences were noticed in the relationship between QT interval and HR.

QRS Duration—The duration of the QRS complexes in all species studied corresponded well with duration in previous reports,^{3,7-10,12-14,16} but all were shorter than was that reported by Malhotra et al¹⁶ for the stump-tail macaque (0.05 s). In the present study, the mean QRS duration for the stump-tail macaque was 0.03 ± 0.01 s.

R-Wave—Although the criteria for low voltage tracings have been set at an R-wave amplitude of less than 1.2 mV in lead II by other authors,^{3,7} R-wave amplitudes seen in the macaques in the present study were consistently less.

The African green and patas monkeys had a higher R-wave amplitude than did the other species studied. Previous data have not been reported for these two species.

T-Wave—The T-wave patterns in the cynomolgus macaque corresponded with those reported for *M. mulatta*.³ Although repolarization abnormalities have been reported,^{3,6,7} they were seldom noticed in this study.

Abnormal Tracings—Left axis deviation was the most frequent abnormality noticed and has been reported in several species.^{3,7,9,10} Varying degrees of bundle branch block have been reported,^{1,3,7,23,24} but occurred infrequently in this study.

Low voltage recordings were noticed in several species in this study and have been reported in rhesus macaques,³ Celebes apes,⁹ and squirrel monkeys.¹²

Premature ventricular contractions were infrequent; this may be because ketamine appears to have a weak antiarrhythmic effect.²⁵ This arrhythmia was relatively frequent in monkeys anesthetized with other agents.^{6,8,12,15}

Ketamine hydrochloride is a safe anesthetic agent for use in nonhuman primates and was found to cause no significant alterations in the ECG of monkeys studied. There was little significant difference in mean values between the *Macaca* spp studied. The New World monkeys (*Saimiri sciureus*, and *Cebus apella*) also tended to have similar mean values.

In general, the data presented were comparable with earlier investigations but incorporated greater numbers of monkeys, including several species not previously reported.

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